Information Disclosure Statement

In response to the Examiner's request, Applicants herewith submit another copy of the Information Disclosure Statement filed December 20, 2001. No Supplemental Information Disclosure Statement was filed in the present application.

Claim Rejections under 35 U.S.C. § 103(a)

Applicants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC (Claim 1). Claim 8 is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% containing less than 0.03% estradiol and less than 0.02% estrone, while Claims 24-25 recite how to achieve the desired purity.

The rejections of Claims 1-13 and 21-25 under 35 U.S.C. § 102(b) over U.S. Patent Nos. 5,504,074 to D'Amato et al. ("*D'Amato*"), 5,521,168 to Clark ("*Clark*"), and 5,643,900 to Fotsis et al. ("*Fotsis*"), and under 35 U.S.C. § 102(e) over U.S. Patent No. 6,200,966 to Stewart et al. ("*Stewart*") were withdrawn in the previous office action. However, Claims 1-13 and 21-25 remain rejected under 35 U.S.C. § 103 as being unpatentable over *D'Amato*, *Clark*, *Fotsis*, or *Stewart*. Applicants respectfully traverse this rejection for the following reasons.

A. The Cited Art Does Not Recognize the Problem

Applicants' written description (page 2, lines 16-27) specifically recognizes the problem of steroid contaminants, such as estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-

methoxyestradiol, estrone, and other estrogenic metabolites, which exhibit estrogenic or carcinogenic effects that counteract the therapeutic effects of 2-methoxyestradiol. *D'Amato*, *Clark*, *Fotsis*, and *Stewart* all fail to recognize this problem. To establish a *prima facie* case of obviousness where the advance lies in the discovery of the problem or the source of the problem, the Examiner would have to provide evidence that a person of ordinary skill in the art at the time of the invention would have expected a problem to exist. *In re Peehs*, 612 F.2d 1287, 204 U.S.P.Q. 835 (CCPA 1980). The Examiner has provided no such evidence, and in fact has *cited art which demonstrates the utility of the very steroid contaminants the Applicants seek to remove.*

Applicants have discovered that the purity of a pharmaceutical composition is critical, as the composition comprising 2-methoxyestradiol must be substantially free of steroid contaminants having estrogenic or carcinogenic effects. Applicants respectfully maintain that the Examiner's assertion of obviousness can only be made with hindsight, using knowledge of Applicants' disclosure. Hindsight is impermissible and only facts gleaned from the cited references themselves may be used in making this determination (MPEP § 2142). As a result, knowledge of Applicants' disclosure must be put aside in making a determination of obviousness (MPEP § 2142).

Accordingly, Applicants respectfully maintain that Claims 1-13 and 21-25 are not rendered obvious by *D'Amato*, *Clark*, *Fotsis*, or *Stewart* under 35 U.S.C. § 103(a) for these reasons, and respectfully request that this rejection be withdrawn and these claims be allowed.

B. The Cited References "Teach Away" from Applicants' Claimed Invention

It is the Examiner's position that obtaining or utilizing a pure form of any pharmaceutical agent would be obvious to the skilled artisan because of the desire to reduce any adverse effect

caused by the contaminant. Applicants respectfully assert that the Examiner's position cannot constitute a proper basis for a rejection under 35 U.S.C. § 103(a), *when the cited art describes these steroid contaminants as desirable or as producing no adverse effects*. Therefore, *none* of the cited references provides any motivation for removing these steroidal contaminants.

U.S. Patent No. 5,504,074 to D'Amato et al. Table 1 (col. 8) of the *D'Amato* patent discloses that estradiol (IC_{50} = 30.0 μM) exhibits the same, desired inhibitory effect on tubulin polymerization as 2-methoxyestradiol (IC_{50} = 1.9 μM), while estrone (IC_{50} > 40 μM) and 4-methoxyestradiol (IC_{50} > 40 μM) exhibit no observed activity within the experimental limits. Thus, the *D'Amato* patent teaches away from Applicants' invention of removing estradiol from a 2-methoxyestradiol composition, and *at best*, suggests that the presence of estrone and 4-methoxyestradiol would impart no effect (other than a simple *dilution* effect) on the activity of the desired compound in a pharmaceutical composition. Nowhere in *D'Amato* is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 5,521,168 to Clark. The structures of preferred estrogen metabolites useful for lowering and controlling intraocular pressure (col. 2, lines 1-21) disclosed in *Clark* include estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol, and 4-methoxyestradiol, each of which the Applicants seek to remove from their claimed composition. Further, *Clark* indicates that the "[m]ost preferred compounds include...2-hydroxyestradiol [and] 4-methoxyestradiol...." (col. 2. lines 22-55). Thus, *Clark* teaches away from Applicants' invention of *removing* estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone from a 2-methoxyestradiol composition. Nowhere in *Clark* is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or

carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 5,643,900 to Fotsis et al. The *Fotsis* patent (Table, col. 3-4; col. 3, lines 31-59) discloses that 4-methoxyestradiol (IC_{50} = 7.24 μM), 2-hydroxyestradiol (IC_{50} = 15.7 μM), estrone (IC_{50} = 26 μM), and estradiol (IC_{50} = 34.5 μM) exhibits the same desired effect on bFGF-induced proliferation of low density bovine capillary endothelial cells (BBCE) *in vitro* as 2-methoxyestradiol. Thus, the *Fotsis* patent teaches away from Applicants' invention of removing 4-methoxyestradiol, 2-hydroxyestradiol, estrone, and estradiol from a 2-methoxyestradiol composition. Nowhere in *Fotsis* is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 6,200,966 to Stewart et al. The *Stewart* patent specifically discloses (col. 6, lines 26-32) that "[f]or the purposes of this specification, the terms 'steroid', 'steroid analogue' or 'steroid-like' are to be understood to encompass 2-methoxyestradiol, 2-hydroxyestradiol, 2-methoxyestradiol-3[-]methyl ether, 4-methoxyestradiol and other compounds based around a steroid nucleus that have the relevant biological activities to be used for the purposes of the present invention." Thus, the *Stewart* patent teaches away from Applicants' invention of removing 2-hydroxyestradiol and 4-methoxyestradiol from a 2-methoxyestradiol composition. Nowhere in *Stewart* is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

Applicants respectfully maintain that the Examiner's basis for rejection of Claims 1-13 and 21-25 under 35 U.S.C. § 103(a) is improper because one skilled in the art would not be motivated to remove these steroidal compounds. None of the *D'Amato*, *Clark*, *Fotsis*, or *Stewart*

patents provides any indication that common steroidal contaminants such as estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol. These steroidal contaminants are described as *desirable* in the cited references, or at worst, as producing no adverse effects, therefore *D'Amato*, *Clark*, *Fotsis*, and *Stewart* all teach away from removing steroid contaminants in 2-methoxyestradiol pharmaceutical compositions.

Accordingly, Applicants respectfully maintain that none of Claims 1-13 and 21-25 is rendered obvious by *D'Amato*, *Clark*, *Fotsis*, or *Stewart* under 35 U.S.C. § 103(a), and respectfully request that this rejection be withdrawn and these claims be allowed.

C. The 2-Methoxyestradiol Composition of *Stewart* Is Not Obtainable in High Purity

Claims 1-13 and 21-25 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over *Stewart* on the basis of the commercially available 2-methoxyestradiol sample obtained from Sigma and used in *Stewart*. It is the Examiner's position that the Sigma Certificate of Analysis discloses the claimed compound can be obtained with a minimum 98% purity, which implies that the compound is *obtainable* in 98-100% purity as determined by HPLC using Sigma's method. Applicants respectfully traverse this rejection under 35 U.S.C. § 103(a), on the basis that the Examiner has improperly inferred an *obtainable upper limit* of purity, from a *Specification* for a *lower limit* of purity.

The Sigma Certificate of Analysis filed as Exhibit A (in the Applicants' Response filed December 14, 2001) shows the 2-methoxyestradiol sold by Sigma Chemical Company can be reproducibly obtained in at least 98.0% purity as determined by HPLC, and indicated in the "Specification" column of the Certificate. This 2-methoxyestradiol sample sold by the Sigma (Lot No. 83H4065 used in *Stewart*) in fact analyzed with a purity of exactly 98.0% as

determined by HPLC (See *"Results"* column of Exhibit A for the actual HPLC purity of 98.0%). The Office Action of August 9, 2002 incorrectly states that the compound utilized in *Stewart* is "obtainable" or "can be obtained" at 100% purity. *The Sigma Certificate of Analysis supports no such conclusion.* Rather, the Certificate of Analysis merely states a lower limit of purity, *not* an obtainable upper limit of purity. Applicants respectfully note that the only inference that can be drawn from this Certificate of Analysis is that 2-methoxyestradiol *cannot* reproducibly be obtained any more pure than the minimum stated Specification of 98%.

Thus, the Sigma Certificate of Analysis *only* supports the fact that up to 2% contamination is an acceptable level in the commercial 2-methoxyestradiol sold by Sigma. Lot No. 83H4065 used in *Stewart* (col. 10, lines 13-17) in fact contains the highest level of 2% contamination. Nothing in *Stewart* or in this Certificate of Analysis supports the notion that a 100% pure product is obtainable using Sigma's method.

Accordingly, Applicants respectfully maintain that none of Claims 1-13 and 21-25 is rendered obvious by *Stewart* under 35 U.S.C. § 103(a), and respectfully request that this rejection be withdrawn and these claims be allowed.

D. One of Ordinary Skill Would Expect Commercial 2-Methoxyestradiol to be Impure

Claims 1-13 and 21-25 are also rejected under 35 U.S.C. § 103(a) over *D'Amato*, *Clark*, *Fotsis*, or *Stewart*, because it is the Examiner's position that the cited references do not show that the recited steroidal contaminants that Applicants seek to remove are actually present in the samples used in these patents. The Examiner states that the ordinary artisan would have the reasonable expectation that the compound is in pure form. Applicants respectfully traverse this rejection and show that one of ordinary skill would instead expect commercially available 2-methoxyestradiol to be impure.

As stated in the Response filed December 14, 2001, *D'Amato*, *Clark*, and *Fotsis* are each completely silent with respect to 2-methoxyestradiol purity. None of these patents describes how the 2-methoxyestradiol was made nor provides any information as to the source of the 2-methoxyestradiol employed in the experiments described therein. Therefore, it may be fairly concluded that the source was commercial and it cannot be assumed that the 2-methoxyestradiol was pure. Indeed, Applicants have examined the purity of commercially available samples of 2-methoxyestradiol (see Table 1 of the Specification, page 18) and shown them to be contaminated with steroidal contaminants.

Further, Applicants respectfully note that synthetic methods for preparing most steroids utilize steroidal precursors, which are subsequently reacted to modify, add, or remove various substituents while maintaining an intact steroid core, while providing the desired compound. As a result, steroidal contaminants, notably estradiol, estrone, and various synthetic intermediates, are typical contaminants in a sample of a target steroid such as 2-methoxyestradiol (Specification page 2, lines 8-15).

Accordingly, Applicants respectfully assert that none of Claims 1-13 and 21-25 is rendered obvious by *D'Amato*, *Clark*, *Fotsis*, or *Stewart* under 35 U.S.C. § 103(a), and respectfully request that this rejection be withdrawn and these claims be allowed.

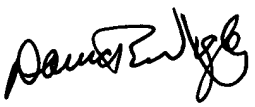
Conclusion

In view of the remarks entered above, Applicants respectfully submit that the claims define patentable subject matter and are in condition for allowance. A Notice of Allowance is therefore requested and such action is respectfully solicited.

If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by

telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is requested. No additional fees are believed due; however, the Commissioner is authorized to charge any deficiencies, or credit any overpayment to deposit account No. 11-0855.

Respectfully submitted,



By: David E. Wigley, Ph.D.
Reg. No. 52,362

Kilpatrick Stockton LLP
Suite 2800
1100 Peachtree Street
Atlanta, GA 30309-4530
Tel. 404.815.6500
Docket No.: 05213-0541 (43170-219662)